

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

1. CERTIFICATE NUMBER: 93-R-0495
CUSTOMER NUMBER: 29767

FORM APPROVED
OMB NO. 0579-0036

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

Pepgen Corporation
1255 Harbor Bay Parkway (b)(2)High, (b)(7)(F)
Alameda, CA 94502

Telephone: (510) -473-0002

A. G. K. Mariano
01/10/06 *mk*

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, or experimentation, or held for these purposes. Attach additional sheets if necessary)

FACILITY LOCATIONS (Sites) - See Attached Listing

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY (Attach additional sheets if necessary or use APHIS Form 7023A)

A. Animals Covered By The Animal Welfare Regulations	B. Number of animal being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals an for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for wh the use of appropriate anesthetic, analgesic, or tranquiliz drugs would have adversely affected the procedures, res or interpretation of the teaching, research, experiments, surgery, or tests. (An explanation of the procedures producing pain or distress in these animals and the reasc such drugs were not used must be attached to this report	F. TOTAL NUMBER OF ANIMALS (COLUMNS C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters		72	55	45	172
8. Rabbits					
9. Non-human Primates					
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

- 1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.
- 2) Each principal investigator has considered alternatives to painful procedures.
- 3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). A summary of all such exceptions is attached to this annual report. In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.
- 4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional Official)

SIGNATURE OF A.E.O. OR INSTITUTIONAL OFFICIAL

NAME & TITLE OF CEO, OR INSTITUTIONAL OFFICIAL (Type or Print)

DATE SIGNED

Stephen L. ...

(b)(6), (b)(7)(c)

Column E Explanation

1. **Registration Number:** 93-R-0495
2. **Number of Animals Used in This Study:** 45
3. **Explain the Procedure producing pain and or distress:**

Syrian golden hamsters (female: weight 65-75 g; Charles River Laboratories) were injected SC with pegylated and non pegylated interferons (IFN's) at a dose range of 10^6 to 10^8 U/Kg. Six to ninety six hours later hamster were inoculated with EMCV IP at a dose range of 1×10^3 to 3×10^3 PFU (300 μ L). Hamsters will be monitored daily for signs of disease and death. Morbidity and mortality rates were used to identify groups with significant treatment effects.

4. **Provide Scientific Justification why pain and/or distress could no be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results**

Rationale for Study

Interferons are a family of functionally related cytokines that confer a range of cellular responses including antiviral, anti-proliferative and immunomodulatory activities. The broad range of cellular activity of IFN's have attracted much interest for clinical applications, with IFN's now being used for to treat a broad range of viral and autoimmune diseases, and cancer. The clinically available forms of human interferons alpha – IFN alpha 2a (Roferon A), IFN alpha 2b (Intron), consensus IFN and pegylated IFN's (PEG-Intron and Pegasys) – are useful in the treatment of several viral diseases and cancer. However, when used at therapeutic doses they produce frequent and sometimes serious side effects, including fever, myalgia, CNS effects and leucopenia, which limit their use. We have synthesized an analog of human INF alpha 2b (Neoferon). Results of our in vitro studies indicated that in contrast to human IFN α 2b, Neoferon was minimally cytotoxic against normal lymphocytes and several human cell lines but retained its in vitro antiviral activity against vesicular stomatitis virus (VSV). The aim of this protocol is to determine the antiviral activity of Neoferon and its pegylated forms and compare the potency to commercially available IFN α 2 (Roferon and Intron A) and its pegylated forms (Pegasys and Peg-Intron A). Our Hypothesis is that the anti-viral effects observed in vitro will extend to in vivo antiviral studies affected by IFN α 2b and that on a per weight basis the relative activity of Neoferon and IFN α 2b, and their pegylated forms will be similar.

Rationale for use of Hamsters:

In general the effects of IFN's on cells of different species in vitro have reflected in vivo efficacy in the corresponding species. In addition most IFN's tend to have species restricted effects. To identify species that would be useful for preclinical evaluation of interferons, Hsu et al., tested the antiviral activity of consensus IFN (CIFN) on cell lines derived from species typically used in preclinical studies, including primate, rabbit, mouse, rat, cat, dog, hamster and guinea pig. The host range of CIFN was found to be similar to that of recombinant human interferon 2 α b. In addition, the use of the Syrian golden hamster for preclinical testing has been reported previously in experiments demonstrating in vivo antiviral activity. These studies showed that hamster are highly susceptible to EMCV infection and different IFN preparations gave a full in vivo response against virus infections. Furthermore, EMCV-infected hamster cells in culture responded to the antiviral effects of IFN's. Therefore, EMCV was chosen for virus challenge studies in hamsters to evaluate different IFN preparation in vivo.

(refs: J. Interferon and Cytokine Research, 15:231-234, 1995; Antimicrobial agents and Chemotherapy, 30(1):52-56, 1986; Antiviral Research, Suppl 1:191-197, J. Interferon Research, 6:405-415, 1986)

Justification why pain and/or distress could not be relieved:

The objective of this study was to generate morbidity and mortality rates for each treatment group. Rates were used to determine efficacy of each test article. No treatment was given for symptoms of disease; any treatment given to ameliorate symptoms would significantly alter the study endpoints (time of disease onset and time of death). Animals were observed twice daily, for signs of disease and deaths. Any animal reported moribund was euthanized immediately.

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